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KENYON & KENYON
1500 K STREET, N.W., SUITE 700
WASHINGTON, DC 20005

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,333	DANENBERG, KATHLEEN D.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6 and 17-27* is/are pending in the application.

4a) Of the above claim(s) *21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,17-20 and 24-27* is/are rejected.

7)☒ Claim(s) *24,25 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/16/02, 9/11/03, 10/3/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Remarks

The Examiner of record has been changed. All further correspondence regarding this application should be directed to Examiner Young J. Kim whose Group Art Unit is 1637.

The Office acknowledges the addition of new claims 17-27 and the cancellation of claims 3, 4, and 7-16.

Claims 21-23 are withdrawn from further consideration.

Claims 1, 5, 6, 17-20, and 24-27 are under prosecution

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-16, and the election of EGFR in the reply filed on October 24, 2004 is acknowledged.

Newly submitted claims 21-23 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 21-23 are drawn to a method of ***treating a metastatic tumor with a chemotherapeutic regimen***. As the method is drawn to a method of treatment, and not a method of determining a regimen (*i.e.*, screening method) as originally claimed, claims 21-23 would require searches and consideration that are not required in a method of screening for a chemotherapeutic regimen.

Accordingly, claims 21-23 are withdrawn from consideration as being directed to a non-elected invention.

Specification

For incorporation by reference to be effective as a proper safeguard against the omission of a portion of a prior application, the incorporation by reference statement ***must be*** included in the ***specification as filed, or transmittal letter-as-filed, or in an amendment specifically referred to in an oath or declaration executing the application***. An incorporation by reference statement added ***after an application's filing date*** is ***not effective because no new matter can be added to an application after its filing date*** (see 35 U.S.C. 132(a)).

If an incorporation by reference statement is included in an amendment to the specification to ***add a benefit claim under 35 U.S.C. 120*** after the filing date of the application, the amendment ***would not be proper***. When a benefit claim under 35 U.S.C. 120 is submitted after the filing date of an application, the reference to the prior application ***cannot include*** an incorporation by reference statement of the prior application. See *Dart Indus v. Banner,* 636 F.2d 684, 207 USPQ 273 (C.A.D.C. 1980).

Applicants are advised to remove the statement, "which are incorporated herein in their entirety by reference thereto," appearing on the priority claim language present on page 1 of the specification (as amended).

Applicants are also advised to peruse the specification and amend in such a way as to insert the appropriate U.S. Application serial number where non-exists but a reference is made. For example, on page 13, line 13, the specification states, "and application 09/_____ (to be assigned)..."

Appropriate correction is required.

Information Disclosure Statement

The IDS received on July 16, 2002, September 11, 2003, and October 3, 2003 are acknowledged. Signed copies of their corresponding PTO-1449 forms are attached hereto.

Drawings

The drawings received on December 3, 2001 are acceptable.

Claim Objections

Claim 24 recites the phrase, "capable of," twice in step (d)(2).

Claim 25 appears to be missing a step-identifier. Specifically, step following the step d-2, appears to be missing a step-identifier d-3.

Claim 27 is a multiple dependent claim, wherein said claim 27 is dependent on one of the withdrawn claims drawn to non-elected invention (*i.e.,* claim 23).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5, 6, 17-20, and 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 17 (and their dependent claims 5, 6, and 18-20) appear to be missing a conjunction between steps b-1 and b-2 (for claim 1) and b-2 and b-3 (for claim 17), rendering the claims indefinite in whether step (b) is complete, resulting in indefinite metes and bounds.

Amending the claims to insert the conjunction, "and" between the above steps would overcome the rejection.

Claim 25 (and its dependent claims 26 and 27) recite the limitation "said isolated and purified oligonucleotide" in step d-3. There is insufficient antecedent basis for this limitation in the claim. Applicants are advised that proper antecedent basis is provided for the phrase, "said oligonucleotide primer."

Claim 25 (and its dependent claims 26 and 27) are also indefinite for the recitation of the phrase "said isolated and purified oligonucleotide" because even if the phrase was interpreted to mean, "said oligonucleotide primer," the term oligonucleotide primer appears in step d-2 as well as step d-3, resulting in the confusion as to which of the two oligonucleotide primers above phrase is referring to.

Claims 1, 17, 24, and 25 (and their dependent claims 5, 6, 18-20, 26, and 27 are indefinite for the recitation of the phrase, "predetermined threshold level for the tumor gene determinant," because it is unclear what this threshold level is for. For example, it is unclear what is determined when the amount of tumor gene determinant mRNA in the primary tumor sample is compared to the predetermined threshold level.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 17, 24, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining a chemotherapeutic regimen for

an individual having a primary and metastatic tumor, wherein said method involves the tumor gene determinant, EGFR (epithelial growth factor receptor), does not reasonably provide enablement for a method for determining a chemotherapeutic regimen for an individual having a primary and metastatic tumor, wherein said method involves **any** tumor gene determinant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Preliminarily, as Applicants elected EGFR for prosecution, the present scope of enablement rejection addresses only the elected subject matter when describing what is enabled for.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

(A) Quantity of experimentation: In order to practice the method for a **single tumor gene determinant**, one skilled in the art must first identify a tumor gene determinant, in order to determine the mRNA expression level of said tumor gene determinant (as required in claim 1(b), which would require empirical determination for determining a tumor gene determinant, designing an oligonucleotide primer pair which would best amplify the tumor gene determinant, followed by establishing a predetermined threshold level for the tumor gene determinant. In order for one skilled in the art to practice the method in commensurate with the scope of the

claims, one skilled in the art would need to repeat the above empirical determination for **every** tumor gene determinant, which would amount to an undue amount of experimentation necessary.

(B) Amount of guidance or directions necessary: The specification appears to give some guidance for a small number of genes which would be useful for tumor gene determinant, such as DPD (dihydropyrimidine dehydrogenase) and TS (thymidylate synthase) (page 11, lines 11-12; pages 27-31), but not a representative number of genes that would adequately guide/direct the one skilled in the art to practice the method in commensurate with the claimed scope.

(C) Presence of Working Examples: As discussed above, the specification only gives examples for EGFR, DPD, and TS tumor gene determinants.

(D) Nature of the invention: The nature of the invention relates to a method of employing a predetermined tumor gene determinant to determine a chemotherpeutic regimen for an individual.

(E) State of prior art: The state of prior art allows a skilled artisan to identify a tumor gene determinant (or marker) only through an empirical determination (see U.S. Patent No. 6,448,041 B1, column 5, lines 44-55).

(F) Skill Level: The relative skill level of a skilled artisan is considered to be high.

(G) Unpredictability of the art: Whether a gene is determined to be useful as tumor gene determinant, absent empirical determination, is highly unpredictable.

(H) The Breadth: The breadth of the claims encompass a method of determining a chemotherapeutic regimen for an individual, wherein said method employs **any** tumor gene determinants.

While the method of identifying a tumor gene determinant requires routine experimentation, in order to practice the claimed method in commensurate with the scope would require a skilled artisan to first identify a representative number of tumor gene determinants (as required by the phrase, "determining mRNA levels of the tumor gene determinant"), which in sheer number of experimentation necessary, would require an undue amount of experimentation. The specification only disclose a few number of tumor gene determinants which would not be representative number of genes, requiring of said skilled artisan an undue amount of experimentation to practice the claimed invention commensurate in scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (c) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 5, and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Kopreski (U.S. Patent No. 6,759,217 B2, issued July 6, 2004, filed September 28, 2001).

Kopreski disclose a method involving determining an expression level of mRNA via RT-PCR, of a tumor gene determinant, EGFR (column 6, lines 51-56), wherein the determination step employs TaqMan® PCR assay (column 8, lines 25-59), which is a fluorescent real-time amplification, wherein the assay inherently involves the comparison of a housekeeping gene (or an internal control) to the marker gene (which is EGFR).

Kopreski also discloses that the markers employed is also useful in that it produces markers for accessing adequacy of anticancer therapy such as surgical intervention, chemotherapy (column 5, lines 28-31), thus anticipating the determination of chemotherapeutic regimen based on the level of EGFR limitation.

Therefore, Koreski anticipates the invention as claimed.

Amending the claims to become drawn to a method involving the use of a pair of oligonucleotide primers of SEQ ID Numbers 1 and 2 would overcome the instant art rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically diselosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subjeet matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to whieh said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17, 18, and 24 are rejected under 35 U.S.C. 103(a) as being obvious over Kopreski (U.S. Patent No. 6,759,217 B2, issued July 6, 2004, filed September 28, 2001, priority March 26, 1996) in view of Danenberg et al. (U.S. Patent No. 6,248,535 B1, issued June 19, 2001, filed December 20, 1999).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of

invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Kopreski disclose a method involving determining an expression level of mRNA via RT-PCR, of a tumor gene determinant, EGFR (column 6, lines 51-56), wherein the determination step employs TaqMan® PCR assay (column 8, lines 25-59), which is a fluorescent real-time amplification, wherein the assay inherently involves the comparison of a housekeeping gene (or an internal control) to the marker gene (which is EGFR).

Kopreski also discloses that the markers employed is also useful in that it produces markers for accessing adequacy of anticancer therapy such as surgical intervention, chemotherapy (column 5, lines 28-31).

Kopreski does not employ the isolation of mRNAs from fixed tumor sample via heating with a chaotrophic agent, wherein the heating occurs at a temperature from about 50°C to about 100 °C (instant claim 17, steps (a) and (b-1)), wherein said fixed tumor sample is paraffin embedding (FPE) (instant claim 24, steps (a)-(d).

Danenberg et al. disclose a method of isolating mRNAs (for RT-PCR reaction) from a paraffin embedded sample (therefore, fixed tumor sample) via heating with a chaotrophic agent, guanidine isothiocyanate, wherein the heating occurs at a temperature from about 60 °C to about 100 °C for about 5 minutes to 2 hours (or 120 minutes) (column 6, lines 36-39); or 75°C to about 100 °C (column 6, lines 49-51), which is well within the instantly claimed range.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Kopreski with the teachings of Danenberg et al. to arrive at the claimed invention for the following reason.

Danenberg et al. disclose that quantitative tissue gene expression have been limited to RT-PCR amplification of RNAs from frozen tissue, which are costly to maintain and transport, raising the need for a simpler and cost-effective method of isolating RNAs from paraffin embedded sample (column 2, lines 1-59).

Therefore, one of ordinary skill in the art at the time the invention was made would have been easily motivated to employ the teachings of Danenberg et al. to practice the method of Kopreski et al., wherein the sample is not only limited to that which was described by Kopreski et al. but also paraffin embedded samples, to take advantage of simpler and cost-effective method of sample preservation and to isolate mRNAs therefrom. As MPEP, at 2143.02, states that the prior art can be modified or combined to reject claims as obvious as long as there is a reasonable expectation of success, one of ordinary skill in the art would have had a reasonable expectation of success in employing the techniques of Danenberg et al. as the artisans isolated the mRNA from PFEs for the purpose of RT-PCR amplification, the same amplification technique employed by Kopreski et al, rendering the claims obvious over the cited references.

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Amending the claims to become drawn to a method involving the use of a pair of oligonucleotide primers of SEQ ID Numbers 1 and 2 would overcome the instant art rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 6, 17-20, and 24-27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,582,919 B2 (issued June 24, 2003, filed June 11, 2001). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The method of claims 1, 5, 6, 17-20, and 24-27 employ the steps of: i) isolating an mRNA from a specimen; ii) determination of the mRNA level of a tumor gene determinant; iii) comparison of the determined amount of the tumor gene determinant to an amount of mRNA of an internal control gene; iv) determining a chemotherapeutic regimen for an individual based on the amount of tumor gene determinant mRNA in the specimen and the predetermined threshold

level for the tumor gene determinant. Some embodiments are drawn to the specimen being fixed and embedded in paraffins (FPE) and the method of preparing the mRNA sample therefrom. An embodiment is drawn to the tumor gene determinant being EGFR. An embodiment is drawn to the use of a specific oligonucleotide primer pairs (SEQ ID Numbers 1 and 2) for amplifying the mRNA of the tumor gene determinant.

The '919 patent claims a method employing the steps of: i) obtaining a tissue sample of a tumor (or specimen) and matching non-malignant sample; ii) isolating mRNA from both tumorigenic and non-malignant samples; iii) amplification of a region of EGFR gene employing a pair of oligonucleotide primers and the determination of the EGFR expression levels; iv) determining a chemotherapeutic regiment via comparison of the EGFR expression level to a threshold level for differential EGFR gene expression.

Claim 5 of the '919 patent employ the same pair of oligonucleotide, namely, oligonucleotides of SEQ ID Number 1 and 2, or their at least 80% homologs, the SEQ ID Numbers of which are identical to the claimed SEQ ID Number 1 and 2 of the instant application (instant claims 19 and 25).

Claim 16 of the '919 patent also employ the specimen from paraffin embedded sample, wherein the temperature range from about 50°C to about 100 °C (claim 27) or from about 75 °C to about 100 °C for a time period of about 5 to about 120 minutes.

As to claims 5 and 20 drawn to a real-time detection. The method of '919 patent, while silent in the claims disclose that TaqMan® is employed for the method (column 13, lines 53-54).

Therefore, the invention as claimed is obvious over the claims of the '919 patent.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (517) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Young J. Kim
Patent Examiner
Art Unit 1637
7/28/04

YOUNG J. KIM
PATENT EXAMINER

yjk